Clinical Trial Protocol

Protocol Title:	A Phase 3, Multicenter, Randomized, Controlled, Double-Masked, Clinical Trial to Evaluate the Efficacy and Safety of OC-01 (varenicline) Nasal Spray on Signs and Symptoms of Dry Eye Disease (The ONSET-2 Study)
Protocol Number:	OPP-101
Study Phase:	3
Product Name:	OC-01 (varenicline) Nasal Spray
[redacted]	[redacted]
Indication:	Dry Eye Disease
Investigators:	Multi-Center
Sponsor:	Oyster Point Pharma, Inc. 202 Carnegie Center Suite 109 Princeton, NJ 08540
Contract Research Organization:	[redacted]
Institutional Review Board:	[redacted]

Date

Original Protocol:	[redacted]
Amendment #1:	[redacted]

Confidentiality Statement

SPONSOR PERSONNEL

[redacted]	[redacted]

MEDICAL MONITOR

Medical Monitor:	[redacted]

SYNOPSIS

Protocol Title:	A Phase 3, Multicenter, Randomized, Controlled, Double-Masked Clinical Trial to Evaluate the Efficacy and Safety of OC-01 (varenicline) Nasal Spray on Signs and Symptoms of Dry Eye Disease (The ONSET-2 Study)
Protocol Number:	OPP-101
Investigational Product:	OC-01 (varenicline) Nasal Spray: • 0.6 mg/mL • 1.2 mg/mL
Study Objective:	The objective of this study is to evaluate the safety and effectiveness of OC-01 (varenicline) Nasal Spray as compared to placebo on signs and symptoms of dry eye disease (DED)
Overall Study Design	
Structure:	A Phase 3, multicenter, randomized, controlled, double- masked study
Duration:	Four (4) study visits over approximately 28 days during the treatment period with three (3) additional long-term follow-up visits at 6 weeks, 6 months, and 12 months.
Control:	Placebo (OC-01 Vehicle Nasal Spray)
Dosing Regimen:	Intranasal delivery of OC-01 twice daily (BID) for 28 days of one of the following dose groups: • 0.6 mg/mL • 1.2 mg/mL • Placebo (vehicle)
Summary of Visit Schedule:	**Visit 1-** Screening and randomization (Day 1) **Visit 2-** Dosing Compliance Assessment (Week 1) **Visit 3-** Schirmer's Score Assessment (Week 2) **Visit 4-** Primary and Secondary Endpoint Assessment • Symptom Assessment (EDS) in Controlled Adverse Environment (CAE) Chamber (Week 4) • Schirmer's Score Assessment; Eye Dryness Score (EDS) Assessment (Week 4) **Visit 5 –** Safety Assessment (Week 6) **Visit 6-** Safety Assessment (Month 6) **Visit 7-** Safety Assessment (Month 12)

Measures Taken to Reduce Bias:	This is a randomized, double-masked study
Study Population Characteristics	
Number of Subjects:	Approximately 750 (250 per treatment arm)
Condition/Disease:	Dry Eye Disease
Inclusion Criteria:	**Subjects must:** 1. [redacted] 2. Have used and/or desired to use an artificial tear substitute for dry eye symptoms within 6 months prior to Visit 1 3. [redacted]

	[redacted]

[1] [redacted]

Exclusion Criteria:	**Subjects must not:** [redacted] 6. Have had any intraocular surgery (such as cataract surgery) or extraocular surgery in either eye within three months or refractive surgery (e.g. laser-assisted in-situ keratomileusis, laser epithelial keratomileusis, photorefractive keratectomy or corneal implant) within twelve months of Visit 1 [redacted] 12. Have a history or presence of any ocular disorder or condition in either eye that would, in the opinion of the Investigator, likely interfere with the interpretation of the study results or participant safety such as significant corneal or conjunctival scarring; pterygium or nodular pinguecula; current ocular infection, conjunctivitis, or inflammation not associated with dry eye; anterior (epithelial) basement membrane corneal dystrophy or other clinically significant corneal dystrophy or degeneration; ocular herpetic infection; evidence of keratoconus; etc. Blepharitis not requiring treatment and mild meibomian gland disease that are typically associated with DED are allowed. [redacted] 14. Have a systemic condition or disease not stabilized or judged by

	the Investigator to be incompatible with participation in the study or with the lengthier assessments required by the study (e.g., current systemic infection, uncontrolled autoimmune disease, uncontrolled immunodeficiency disease, history of myocardial infarction or heart disease, etc.) 15. Have a known hypersensitivity to any of the procedural agents or study drug components [redacted] 18. Have any condition or history that, in the opinion of the investigator, may interfere with study compliance, outcome measures, safety parameters, and/or the general medical condition of the subject [redacted]

Study Formulations:	Subjects will be randomized 1:1:1 to be treated with OC-01 (varenicline) Nasal Spray delivered as a 50 microliter (µL) spray in each nostril at the following formulations: • 0.6 mg/mL • 1.2 mg/mL • Placebo (vehicle)
Randomization:	The randomization will be stratified by three factors: • Pre-procedure (Baseline) anesthetized Schirmer's score (≤5, >5) measured the screening/randomization visit • Pre-procedure (Baseline) EDS (<60, ≥60) measured at the screening/randomization visit • Study site A central randomization list will be created using block randomization. Sites will be assigned entire blocks as needed.
Evaluation Criteria	
Efficacy Measures:	**Primary Endpoint:** • Percent of subjects who achieve ≥10 mm improvement in Schirmer's Test Score from baseline at Visit 4 (Day 28) **Secondary Endpoints** • Mean change from Baseline in Eye Dryness Score (EDS) at 5 minutes after threshold defined treatment administration in the Controlled Adverse Environment® Chamber at Visit 4 (Day 28) • Mean change from Baseline in Eye Dryness Score (EDS) at Visit 4 (Day 28) (Post STS) • Mean change from Baseline in Schirmer's Test Score (STS) at Visit 4 (Day 28). • Mean change from Baseline in Corneal Fluorescein Staining at Visit 4 (Day 28)
Safety Measures:	• Adverse Event (AE) Query • Intranasal Exam • Slit Lamp Biomicroscopy
Other Efficacy Measures:	N/A

Summary of Known and Potential Risks and Benefits to Human Subjects

The administration of OC-01 0.6 mg/mL and 1.2 mg/mL (varenicline) Nasal Spray was safe, well tolerated, and efficacious as assessed in the ONSET-1 study. The study met the primary endpoint (Schirmer's Test) for both the 0.6 mg/mL and 1.2 mg/mL dose groups. It also met the secondary symptom endpoints (EDS) for 0.6 mg/mL OC-01 (varenicline) Nasal Spray. There was not a statistically significant improvement in EDS in the normal environment at Day 28 for the 1.2 mg/mL dose, although there was a numerical benefit as compared to placebo. Because of the pre-specified hierarchical approach to multiplicity for the secondary outcomes, the EDS symptoms within the CAE® environment at Day 21 could not be formally tested; however, the data strongly suggest benefit on that outcome as well. Although the low dose of 0.12 mg/mL OC-01 (varenicline) Nasal Spray demonstrated statistical significance in Schirmer's Score in exploratory analyses, this dose did not yield statistically significant difference in the symptom endpoint in exploratory analyses as measured by EDS.

Showing statistical significance in both signs and symptoms of DED in the same study population is a goal seldom before achieved in the treatment of the disease. Importantly, after treatment with OC-01 (varenicline) Nasal Spray, improvements in EDS were seen as early as 5 minutes after administration in the CAE® in the 0.6 mg/mL and 1.2 mg/mL OC-01 (varenicline) Nasal Spray dose groups. Exploratory analyses of fluorescein corneal staining indicate a benefit in subjects treated with OC-01 (varenicline) Nasal Spray compared to those subjects treated with placebo.

OC-01 (varenicline) Nasal Spray was safe and well-tolerated at all concentrations assessed in the ONSET-1 clinical study. Most TEAEs were mild to moderate in severity, with only 1 subject reporting a severe TEAE.

The most common AE in all treatment groups was sneezing which was temporally related to the administration of the study drug and resolved within a short period of time after administration. Sneezing AEs were characterized as mild to moderate, with no severe AEs reported.

All AEs that were suspected to be related to the study drug with the exception of AEs with each of the following terms; nasal dryness, nasal congestion and throat irritation were reported to be recovered/or resolved before study completion. Eleven ocular TEAEs were reported, 7 of which were reported in the placebo group; all other AEs were classified as non-ocular. The Investigators considered 3 of the 7 ocular TEAEs (visual acuity reduced, conjunctival hemorrhage, and eyelid oedema) to be possibly related to study drug, all resolved, and none was categorized as severe. One treatment-emergent SAE (anemia) was reported and was considered to be unrelated to study drug. No treatment-related treatment-emergent SAEs were observed. No deaths occurred during the study. Visual acuity, slit-lamp biomicroscopy, intranasal examination, and pupil diameter did not indicate clinically significant changes from baseline. These data from the ONSET-1 study suggest that 28 days of BID delivery of OC-01 (varenicline) Nasal Spray is safe and efficacious in subjects with DED.

LIST OF ABBREVIATIONS

AE	Adverse event
ANCOVA	Analysis of covariance
BCVA	Best corrected visual acuity
BID	Two times a day
CAE®	Controlled adverse environment
CFR	Code of Federal Regulations
CI	Confidence interval
CRF	Case report form
eCRF	Electronic Case Report Form
EDS	Eye Dryness Score
DED	Dry eye disease
HIPAA	Health Information Portability and Accountability Act
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Conference on Harmonisation
IRB	Institutional Review Board
ITT	Intention to Treat
logMAR	Logarithm of the minimum angle of resolution
LS	Least Square
MAD	Mucosal Atomization Device
MedDRA	Medical Dictionary for Regulatory Activities
MI	Multiple imputation
mg	Milligram
mL	Milliliter
µL	microliter
mm	Millimeter
nAChR	Nicotinic acetylcholine receptor
OSDI©	Ocular Surface Disease Index©
PP	Per Protocol
SAE	Serious adverse event
SAP	Statistical Analysis Plan
STS	Schirmer's Test Score
TEAE	Treatment-emergent adverse event
US	United States

1 INTRODUCTION

Dry eye disease (DED) is a multifactorial, age-related disorder of the ocular surface resulting

[redacted]

[redacted]

2 STUDY OBJECTIVES

The objective of this study is to evaluate the safety and effectiveness of OC-01 (varenicline) Nasal Spray as compared to placebo on signs and symptoms of dry eye disease (DED).

3 CLINICAL HYPOTHESES

This study is testing the hypothesis that OC-01 (varenicline) Nasal Spray is superior to placebo in treating the signs and symptoms of DED.

4 OVERALL STUDY DESIGN

Protocol OPP-101 is a Phase 3, multicenter, randomized, controlled, double- masked study designed to evaluate the safety and efficacy of OC-01 (varenicline) Nasal Spray in adult participants with DED. Approximately 750 subjects at least 22 years of age with a physicians' diagnosis of dry eye disease and meeting all other study eligibility criteria will be randomized to receive an application of OC-01 (varenicline) Nasal Spray or placebo twice daily (BID) for 28 days with three additional long-term follow-up visits at 6 weeks, 6 months and 12 months.

Participants who terminate early during the application period will be asked to complete safety assessments (if the participants agree) prior to study exit. Participants who are terminated early from the study will not be replaced.

5 STUDY POPULATION

5.1 Number of Subjects

Approximately 750 participants (approximately 250 per arm) will be enrolled in approximately 25 sites in the US. Subjects will be randomized 1:1:1 to receive one of the following three dose assignments. All doses will be delivered as a 50 microliter (µL) intranasal spray in each nostril BID for a total of 28 days:

- Placebo (vehicle) [control]
- OC-01 (varenicline) Nasal Spray, 0.6 mg/mL
- OC-01 (varenicline) Nasal Spray, 1.2 mg/mL

5.2 Study Population Characteristics

All subjects must be at least 22 years of age, of either gender, and of any race, and must meet all inclusion criteria and none of the exclusion criteria.

5.3 Inclusion Criteria

Subjects must:

1. [redacted]
2. Have used and/or desired to use an artificial tear substitute for dry eye symptoms within 6 months prior to Visit 1
3. [redacted]

4. [redacted]

5.4 Exclusion Criteria

Subjects must not:

[redacted]

6. Have had any intraocular surgery (such as cataract surgery) or extraocular surgery in either eye within three months or refractive surgery (e.g. laser-assisted in-situ keratomileusis, laser epithelial keratomileusis, photorefractive keratectomy or corneal implant) within twelve months of Visit 1

[redacted]

12. Have a history or presence of any ocular disorder or condition in either eye that would, in the opinion of the Investigator, likely interfere with the interpretation of the study results or participant safety such as significant corneal or conjunctival scarring; pterygium or nodular pinguecula; current ocular infection, conjunctivitis, or inflammation not associated with dry eye; anterior (epithelial) basement membrane corneal dystrophy or other clinically significant corneal dystrophy or degeneration; ocular herpetic infection; evidence of keratoconus; etc. Blepharitis not requiring treatment and mild meibomian gland disease that are typically associated with DED are allowed.

[redacted]

14. Have a systemic condition or disease not stabilized or judged by the Investigator to be incompatible with participation in the study or with the lengthier assessments required by the study (e.g., current systemic infection, uncontrolled autoimmune disease, uncontrolled immunodeficiency disease, history of myocardial infarction or heart disease, etc.)
15. Have a known hypersensitivity to any of the procedural agents or study drug

components

16. [redacted]

18. Have any condition or history that, in the opinion of the investigator, may interfere with study compliance, outcome measures, safety parameters, and/or the general medical condition of the subject

[redacted]

5.5 Withdrawal Criteria

If at any time during the study the Investigator determines that a subject's safety has been compromised, the subject may be withdrawn from treatment, but will be followed for safety for the duration of the study, unless they refuse to attend follow-up visits. Subjects will be asked to attend Visit 4b, Visit 5, Visit 6 and Visit 7 for endpoint and safety assessments.

Subjects may withdraw consent from the study at any time.

Sponsor and/or Investigator may discontinue any subject from study treatment for non-compliance or any valid medical reason during the course of the study (see Section 8.6.2).

6 STUDY PARAMETERS

6.1 Efficacy Measures

6.1.1 Primary Efficacy Measure

The following primary endpoints will be tested:

- Percent of subjects who achieve ≥10 mm improvement in Schirmer's Test Score (STS) from baseline at Visit 4 (Day 28)

6.1.2 Secondary Efficacy Measure

- Mean Change from Baseline in Eye Dryness Score (EDS) at 5 minutes after threshold defined treatment administration in the Controlled Adverse Environment® Chamber at Visit 4 (Day 28)
- Mean Change from Baseline in Eye Dryness Score (EDS) at Visit 4 (Day 28) (Post STS)
- Mean Change from Baseline in Schirmer's Test Score (STS) at Visit 4 (Day 28)
- Mean Change from Baseline in Corneal Fluorescein Staining at Visit 4 (Day 28)

6.2 Safety Measures

- Adverse Events
- Intranasal Exam
- Slit Lamp Biomicroscopy

6.3 Other Measures

- Urine pregnancy test (Visit 1 and Visit 4a/ET)

7 STUDY MATERIALS

7.1 Study Drug(s)

7.1.1 Regimens

The study drug will be delivered as a 50 microliter (µL) intranasal spray in each nostril BID:

- OC-01 (varenicline) Nasal Spray, 0.6 mg/mL
- OC-01 (varenicline) Nasal Spray, 1.2 mg/mL
- Placebo (vehicle)

7.1.2 Dispensation Schedule

- At Visit 1, qualified subjects will be randomized and the first dose of study drug will be administered in office concurrent with Schirmer's test. The second daily administration will happen at home.
- At Visit 2, study drug/placebo will not be administered in office. Subject will self-administer study drug/placebo following their routine schedule.
- At Visit 3 the first daily dose of study drug will be administered in office concurrent with Schirmer's testing. The second daily administration will happen at home.
- At Visit 4a subjects will receive their first daily dose of study drug during CAE® exposure. The second daily administration will happen at home.
- At Visit 4b the first daily dose of study drug will be administered in office concurrent with Schirmer's testing.
- Between clinic visits, subjects will self-administer OC-01 (varenicline) Nasal Spray BID as a 50 µL dose in each nostril.

7.1.3 General Appearance

- OC-01 (varenicline) /Placebo Nasal Spray will be formulated at the desired concentration in sodium phosphate buffers and sodium chloride as an aqueous solution, and presented in a multi-use preservative-free nasal pump.
- The product is preservative-free and intended for intranasal use only. The product should not be used if cloudy or if particulate matter is present.
- OC-01 (varenicline) solution must be administered without dilution.

7.2 Other Study Supplies

For all other study supplies refer to the Non-IP supplies list.

8 STUDY METHODS AND PROCEDURES

8.1 Participant Entry Procedures

8.1.1 Overview

Participants as defined by the criteria in Sections 5.2, 5.3, and 5.4 will be considered for entry into this study.

8.1.2 Informed Consent

Prior to a participant's enrollment in the trial (i.e., prior to any study-related procedures), the study will be discussed with each potential participant and participants wishing to participate must be administered and provide written informed consent using an Institutional Review Board (IRB)-approved informed consent form (ICF). The ICF must be the most recent version that has received approval by a properly constituted IRB.

8.1.3 Washout Intervals

Prohibited medications, treatments, and activities are outlined in the Exclusion Criteria (Section 5.4).

8.1.4 Procedures for Final Study Entry

Subjects must meet all inclusion criteria and none of the exclusion criteria.

8.1.5 Methods for Assignment to Treatment Groups

Each subject who enters the screening period for the study (defined as the point at which the subject signs the informed consent form (ICF) receives a unique subject identification number before any study-related activities/procedures are performed. This number will be used to identify the subject throughout the clinical study and must be used on all study documentation related to that subject.

The subject identification number must remain constant throughout the entire clinical study.

Subjects who meet the eligibility requirements will be randomly assigned to 1 of 3 treatment groups.

The randomization will be stratified by three factors:

- Pre-procedure (Baseline) anesthetized Schirmer's score ($\leq$5, >5) measured the screening/randomization visit
- Pre-procedure (Baseline) EDS (<60, $\geq$60) measured at the screening/randomization visit
- Study site

A central randomization list will be created using block randomization. Sites will be assigned entire blocks as needed.

8.2 Concomitant Therapies

The use of any concurrent medication, prescription or over-the-counter, is to be recorded on the subject's source document and corresponding eCRF along with the reason the medication was taken.

Concurrent enrollment in another investigational drug or device study during the treatment period is not permitted.

8.2.1 Prohibited Medications/Treatments

Disallowed medications/treatments during the study are outlined in the Exclusion Criteria below:

- No concomitant use of a nicotinic acetylcholine receptor agonist [Nicoderm®, Nicorette®, Nicotrol NS® (nicotine), Tabex®, Desmoxan® (cytisine), and Chantix® (varenicline)] during the treatment period (Baseline to Day 28) of the study.
- No concomitant use of Restasis® or Xiidra® during the treatment period (Baseline to Day 28) of the study.

8.2.2 Escape Medications

No escape medication is required for this study.

8.2.3 Special Diet or Activities

No special diets or activity is required for this study.

8.3 Examination Procedures

8.3.1 Procedures to be Performed at Each Study Visit with Regard to Study Objectives(s)

The following procedures will be performed (see Appendix 2 for description).

Screening/Visit 1 (Day 1): Screening and Randomization

- Informed consent/Health Information Portability and Accountability Act (HIPAA) consent
- Demographic data, medical history, prior medication (s), and ocular history
- Eligibility Criteria
- Urine pregnancy test (if applicable)
- OSDI© questionnaire
- Eye Dryness Scale (EDS) (visual analog scale) (pre-treatment)
- [redacted] Ocular Discomfort Scale (pre-treatment)
- BCVA (pre-and post-treatment procedures)
- Slit lamp biomicroscopy (pre-and post-treatment procedures)
- Corneal fluorescein staining
- Baseline Schirmer's Test
- Schirmer's Test with nasal stimulation (cotton swab)[3]
- Intranasal examination (pre-and post-treatment procedures)
- Randomization
- Dispense study drug/placebo
- Schirmer's Test (concurrent with treatment)[2]
- Administration of study drug/placebo concurrently with Schirmer's Test
- Concomitant Medications
- AE Query

[2] Procedure will occur after corneal fluorescein staining

[3] Schirmer's test with nasal stimulation will occur ≥10 minutes after the Baseline Schirmer's test

Visit 2 (Day 7 ±2): Dosing Compliance Assessment

- BCVA
- EDS (visual analog scale)
- Slit lamp biomicroscopy
- Intranasal exam
- Concomitant Medications
- AE Query

Visit 3 (Day 14 ±3): Schirmer's Test Assessment

- EDS (visual analog scale)
- BCVA (pre-and post-treatment)
- Slit lamp biomicroscopy (pre-and post-treatment)
- Administration of study drug/placebo
- Schirmer's Test (concurrent with treatment)
- Dispense study drug/placebo
- Concomitant Medications
- AE Query

Visit 4 (Day 28 ±4): Primary and Secondary Endpoint Assessment
Visit 4 CAE® and Schirmer's Test Evaluation procedures are conducted on different days within the visit window. The Schirmer's Test Evaluation and all assessments should be performed after the CAE® visit assessments.

Visit 4a
Pre- CAE® Procedures:

- Urine pregnancy test (if applicable)
- EDS (visual analog scale)
- [redacted] Ocular Discomfort Scale
- BCVA
- Dispense study drug/placebo
- Concomitant Medications
- AE Query

Pre-Treatment CAE® Evaluation

- EDS (visual analog scale)
- [redacted] Ocular Discomfort Scale until threshold is met

ADMINISTRATION OF INVESTIGATIONAL DRUG/PLACEBO

Treatment with Investigational drug/placebo will be administered upon a participant's reporting an Ocular Discomfort score ≥ 3 at two or more consecutive time points in at least one eye during CAE® exposure (participants with an Ocular Discomfort rating of 3 at time = 0 for an eye must report an Ocular Discomfort rating of 4 for two consecutive measurements for that eye (i.e. Threshold). Participants with an Ocular Discomfort rating of 4 at time = 0 for an eye must report an Ocular Discomfort rating of 4 for two additional consecutive measurements for that eye, not including time = 0 measurement) using the [redacted] Scale. Participants will resume symptom assessments (EDS and ODS) every 5 minutes starting 1 minute after the application ends.

Post-Treatment CAE® Evaluation

- EDS (visual analog scale)
- [redacted] Ocular Discomfort Scale

Visit 4b (Minimum +3 Days after Visit 4a)
Schirmer's Test Evaluation:

- EDS (visual analog scale) (post treatment)
- BCVA (pre and post treatment)
- Slit lamp biomicroscopy (pre and post treatment)
- Corneal fluorescein staining (post treatment)
- Intranasal examination (pre and post treatment)
- Administration of study drug/placebo
- Schirmer's Test (concurrent with treatment)
- Concomitant medications
- AE Query

Visit 5 (Day 42 ± 3): 6 Week Safety Assessment

- Slit lamp biomicroscopy
- Intranasal examination
- Concomitant Medications
- AE Query

Visit 6 (Day 168 ± 7): 6 Month Safety Assessment

- Slit lamp biomicroscopy
- Intranasal examination
- Concomitant Medications
- AE Query

Visit 7 (Day 336 ±7): 12 Month Safety Assessment

- Urine pregnancy test (if applicable)

- Slit lamp biomicroscopy
- Intranasal examination
- Concomitant Medications
- AE Query

8.4 Schedule of Visits, Measurements and Dosing

8.4.1 Scheduled Visits

Refer to Appendix 1 for a schedule of visits and measurements.

8.4.2 Unscheduled Visits

These visits may be performed in order to ensure subject safety. All procedures performed at an unscheduled visit will be recorded in the source documents and on the Unscheduled Visit eCRF pages. Any procedure indicated in the eCRF that is not performed should be indicated as "Not done."

Evaluations that may be conducted at an Unscheduled Visit include:

- Slit-lamp Biomicroscopy;
- EDS
- BCVA
- Intranasal Examination;
- Corneal Fluorescein staining
- Urine Pregnancy Test (if applicable);
- Assessment of AEs;
- Assessment of concomitant medications and/or treatments; and
- Any other assessments needed in the judgment of the investigator.

8.5 Compliance with Protocol

Subjects will be instructed on the proper use and storage of the study drug at Visits 1, 2, 3 and 4a, and provided with written instructions upon dispensation of their study drug at Visit 1..

8.6 Subject Disposition

8.6.1 Treatment Completed Subjects

A Treatment Completed Subject is one who has completed the first 4 weeks of study visits.

8.6.2 Safety Follow up Completed Subjects

A Safety Follow up Completed Subjects is one who has completed all study visits up to Visit 7.

8.6.3 Discontinued Subjects

Subjects may be discontinued from treatment, or from involvement in the study at any time prior to their completion of the study due to:

- Non-Fatal Adverse Event;
- Protocol Violations;
- Lost to Follow-up;
- Physician Decision;
- Subject Non-compliance;
- Death;
- Study Terminated by sponsor;
- Withdraw by Subject (e.g. withdrawal of consent); and
- Other

Note: In addition, any subject may be discontinued from treatment or from study involvement from any sound medical reason at the discretion of the investigator (after consultation with the Sponsor) or Sponsor.

Notification of a subject discontinuation and the reason for discontinuation will be made to [redacted] and/or Sponsor and will be clearly documented on the eCRF.

If the subject discontinues from treatment, they will be asked to be followed for safety for the duration of the study, unless they refuse to attend follow-up visits. Subjects will be asked to attend Visit 4b, Visit 5, Visit 6 and Visit 7 and have all scheduled assessments performed as per the Schedule of Visits and Measurements (Appendix 1)

Discontinued subjects will not be replaced.

8.7 Study Termination

The study may be stopped at any time by the Investigator and/or [redacted] after consultation with the Sponsor, with appropriate notification.

8.8 Study Duration

An individual subject's participation will involve 7 visits over approximately 48-weeks (336 days)

8.9 Monitoring and Quality Assurance

During the course of the study a monitor, or designee, will make routine site visits to review protocol compliance, assess study drug accountability, subject safety, and ensure the study is being conducted according to the pertinent regulatory requirements. The review of the subjects' medical records will be performed in a manner that adequately maintains subject confidentiality. A monitoring plan will outline further details of the study monitoring.

Regulatory authorities of domestic and foreign agencies, Sponsor quality assurance, [redacted]. quality assurance and or its designees may carry out on-site inspections and/or audits, which may include source data checks. Therefore, direct access to the original source data will be required for inspections and/or audits. All inspections and audits will be carried out giving consideration to data protection as well as subject confidentiality to the extent that local, state, and federal laws apply.

9 SAFETY DEFINITIONS, SAFETY MONITORING AND REPORTING

9.1 Adverse Event

An adverse event (AE) is defined as any untoward medical occurrence associated with the use of a drug in humans, whether or not the event is considered drug-related. An AE can therefore be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease occurring after the subject started dosing with the study drug, without any judgment about causality. Any pre-existing medical condition that worsens after administration of the study drug will also be considered a new AE.

Study drug includes the investigational drug under evaluation and placebo.

AE collection will start following the first administration of study drug until the last follow up visit of the study.

Documentation regarding the AE should be made as to the nature, date of onset, end date, severity, relationship to study drug, action(s) taken, seriousness, and outcome of any sign or symptom observed by the Investigator or reported by the subject upon indirect questioning.

9.1.1 Severity

Severity of an AE is defined as a qualitative assessment of the degree of intensity of an AE as determined by the investigator or reported to him/her by the patient/subject. The assessment of severity is made irrespective of relationship to study drug or seriousness of the event and should be evaluated according to the following scale:

- *Mild:* Event is noticeable to the subject but is easily tolerated and does not interfere with the subject's daily activities.
- *Moderate*: Event is bothersome, possibly requiring additional therapy, and may interfere with the subject's daily activities.
- *Severe*: Event is intolerable, necessitates additional therapy or alteration of therapy, and interferes with the subject's daily activities.

9.1.2 Relationship to Study Drug

The relationship of each AE to the investigational product should be determined by the investigator (in a blinded manner) using these explanations:

- *Definite:* When there are good reason and sufficient documentation to demonstrate a direct causal relationship between investigational product and AE

- *Probable:* When there are good reasons and sufficient documentation to assume a causal relationship in the sense of plausible, conceivable, likely but not necessarily highly probable
- *Possible:* When there is sufficient information to accept the possibility of a causal relationship in the sense of not impossible and not unlikely, although the connection is uncertain or doubtful, for example; due to missing data or insufficient evidence.
- *None:* When there is sufficient information to accept a lack of a causal relationship, in the sense of impossible and improbable.
- *Unclassified:* When the causal relationship is not assessable for whatever reason due to insufficient evidence, conflicting data or poor documentation.

9.1.3 Expectedness

The expectedness of an AE should be determined based upon existing safety information about the study drug using these explanations:

- *Unexpected:* An AE that is not listed in the Investigator's Brochure (IB) or is not listed at the specificity or severity that has been observed.
- *Expected:* An AE that is listed in the IB at the specificity and severity that has been observed.
- *Not Applicable:* Any AE that is unrelated to the study drug.

AEs that are mentioned in the IB as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug but are not specifically mentioned as occurring with the particular drug under investigation are to be considered unexpected.

The investigator should initially classify the expectedness of an AE, but the final classification is subject to the Medical Monitor's determination.

9.2 Serious Adverse Events

An AE is considered "serious" (SAE) if, in the view of either the investigator or Sponsor, it results in any of the following outcomes:

- Death
- A life-threatening AE

  Note: An AE is considered "life-threatening" if, in the view of either the investigator or Sponsor, its occurrence places the patient or subject at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death.
- Inpatient hospitalization or prolongation of existing hospitalization

Note: The term "inpatient hospitalization" refers to any inpatient admission (even if less than 24 hours). For chronic or long-term inpatients, inpatient admission includes transfer within the hospital to an acute/intensive care inpatient unit. Inpatient hospitalization does not include: emergency room visits; outpatient/same-day/ambulatory procedures; observation/short stay units; rehabilitation facilities; hospice facilities; nursing homes; or clinical research/phase 1 units.

Note: The term "prolongation of existing hospitalization" refers to any extension of an inpatient hospitalization beyond the stay anticipated or required for the reason for the initial admission as determined by the investigator or treating physician.

- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions

  Note: An SAE specifically related to visual threat would be interpreted as any potential impairment or damage to the subject's eyes (e.g., hemorrhage, retinal detachment, central corneal ulcer or damage to the optic nerve).

- A congenital anomaly/birth defect in an offspring of a study subject.

Important medical events that may not result in death, are life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

SAEs are collected at the time the subject signs the Informed Consent Form until the last follow up visit of the study.

9.3 Procedures for Reporting Adverse Events

All AEs and their outcomes must be reported to [redacted] the Sponsor, and the IRB/IEC as required by the IRB/IEC, federal, state, or local regulations and governing health authorities and recorded on the appropriate eCRF.

9.3.1 Reporting a Suspected Unexpected Adverse Reaction

All AEs that are 'suspected' and 'unexpected' are to be reported to [redacted] the Sponsor and the IRB/IEC as required by the IRB/IEC, federal, state, or local regulations and governing health authorities.

9.3.2 Reporting a Serious Adverse Event

To ensure subject safety, all SAEs, regardless of relationship to the study drug, must be immediately reported. All information relevant to the SAE must be recorded on the appropriate CRFs. The investigator is obligated to pursue and obtain information requested by [redacted] and/or the Sponsor in addition to that information reported on the CRF. All subjects experiencing a SAE must be followed up and the outcome reported.

In the event of a SAE, the investigator must notify [redacted] and the Sponsor immediately; obtain and maintain in his/her files all pertinent medical records, information, and medical judgments from colleagues who assisted in the treatment and follow-up of the subject; provide[redacted] and the Sponsor with a complete case history, which includes a statement as to whether the event was or was not suspected to be related to the use of the study drug; and inform the IRB of the SAE within their guidelines for reporting SAEs.

Contact information for reporting SAEs:

Name: Title: Company: Office Telephone: Mobile Telephone: Office Facsimile:	[redacted] Clinical Project Manager[redacted] [redacted]
Name: Title: Office Telephone: Mobile Phone: Office Facsimile:	[redacted] Medical Monitor [redacted]

9.4 Procedures for Unmasking of Study Drug

All subjects, investigators, and study personnel involved with the conduct of the study will be masked with regard to treatment assignments. When medically necessary, the investigator may need to determine what treatment regimen has been assigned to a subject. When possible (i.e., in non-emergent situations), [redacted] and/or the Sponsor should be notified before unmasking study drug. Unmasking will be performed utilizing the randomization system. The unmasked subject will continue the study if warranted by the Investigator in consultation with the Medical Monitor.

9.5 Type and Duration of the Follow-up of Subjects after Adverse Events

The investigator will follow unresolved AEs to resolution until the subject is lost to follow-up or until the AE is otherwise classified. Resolution means the subject has returned to baseline state of health or the Investigator does not expect any further improvement or worsening of the AE. If the patient is lost to follow-up, the Investigator should make 3 reasonable attempts to contact the patient via telephone, post, or certified mail. All follow-up

will be documented in the subject's source document. Non-serious AEs identified on the last scheduled contact must be recorded on the AE eCRF with the status noted.

If the Investigator becomes aware of any new information regarding an existing SAE (i.e., resolution, change in condition, or new treatment), a new SAE/Unanticipated Report Form must be completed and faxed to [redacted] within 24 hours of the site's awareness of the new information. The original SAE form is not to be altered. The report should describe whether the event has resolved or continues and how the event was treated.

10 STATISTICAL ANALYSIS

Statistical considerations and methods of analyses for this study are provided below; the accompanying Statistical Analysis Plan (SAP) contains complete details of the planned analyses.

10.1 Primary and Secondary Endpoints

Primary Endpoint:

- Percent of subjects who achieve ≥10 mm improvement in Schirmer's Test Score from baseline at Visit 4 (Day 28)

Secondary Endpoints

- Mean change from Baseline in Eye Dryness Score (EDS) at 5 minutes after threshold defined treatment administration in the Controlled Adverse Environment® Chamber at Visit 4 (Day 28)
- Mean change from Baseline in Eye Dryness Score (EDS) at Visit 4 (Day 28) (Post STS)
- Mean change from Baseline in Schirmer's Test Score (STS) at Visit 4 (Day 28)
- Mean change from Baseline in Corneal Fluorescein Staining at Visit 4 (Day 28)

10.2 Analysis Populations

10.2.1 Intention-To-Treat Population

The intent-to-treat (ITT) population will include all randomized subjects. Analyses using the ITT population will group subjects according to the treatment to which they were randomized.

10.2.2 Safety Population

The safety population will include all randomized subjects who received at least one dose of the study drug. Analysis on the safety population will group subjects according to the treatment actually received.

10.3 Statistical Hypotheses

Let p_l, p_h, and p_p denote the percent of subjects in each group (low dose, high dose, and placebo, respectively) who have $\geq$ 10mm change from baseline to Visit 4 in STS.

H_0: $p_l - p_p = 0$ or $p_h - p_p = 0$

H_1: $p_l - p_p \neq 0$ or $p_h - p_p \neq 0$

10.4 Sample Size and Power Considerations

The study will randomize approximately 750 subjects in a 1:1:1 ratio to the three treatment groups. Approximately 250 subjects in each treatment group are expected to complete their assigned treatment and have endpoint assessments at Visit 4.

For the primary endpoint, the percent of subjects achieving $\geq$ 10 mm improvement from Baseline in STS at Visit 4, the ONSET-1 study had roughly 15% of subjects in the placebo group and 50% in each of the 0.6 mg/ml and 1.2 mg/ml groups. If the true proportion achieving at least a 10 mm improvement is 15% in the placebo group and, conservatively, 40% in each of the active arms, the power for each dose would be greater than 99%.

The secondary endpoint is the EDS test. The ONSET-1 study showed a roughly 12 unit difference between placebo and each active treatment group in mean change from baseline to day 28 with a standard deviation (SD) of roughly 26 units. If these estimates apply to the Phase III ONSET-2 study and the data are analyzed with an analysis of variance, the study will have approximately 99% power for each dose.

10.5 Statistical Analysis

This section briefly outlines the planned efficacy analyses. The statistical analysis plan (SAP) describes the methods to be used in detail. If the SAP and the protocol disagree, the details and methods of the SAP will prevail.

10.5.1 General Considerations

Quantitative variables will be summarized using the number of subjects (n), mean, SD, median, 25th and 75th percentiles, and minimum and maximum. Qualitative variables will be summarized using counts and percentages.

All summaries will be presented by treatment group. Summaries will be provided for demographics, medical history, concomitant medications, and subject disposition.

For the summaries, medical history, concomitant medications, and AEs will be coded to MedDRA and World Health Organization Drug dictionaries, as appropriate.

Baseline measures are defined as the last measure prior to the initiation of study treatment, usually at Visit 1 screening.

10.5.2 Unit of Analysis

For efficacy endpoints, the unit of analysis will be the study eye as defined as the eye that meets all inclusion and no exclusion criteria. If both eyes qualify, then the study eye will be the eye with the greatest increase in tear production with stimulation by a cotton swab at the Screening Visit. If there is no difference in stimulated tear production, the study eye will be the eye with the lower basal Schirmer's Test Score at screening. If there is no difference for either measure, the right eye will be used as the study eye.

For safety endpoints, both eyes will be analyzed.

10.5.3 Subject Demographics and Baseline Characteristics

Continuous summary statistics will be generated for age in years by treatment group and for all subjects. Discrete summary statistics will be generated for the following qualitative demographic variables: age category, gender, ethnicity, race, and other baseline intranasal examination results, tabulated by treatment group and for all subjects. Individual subject data listings will support the Summary tables.

10.5.4 Primary Efficacy Analysis

[redacted]

10.5.5 Secondary Efficacy Analysis

[redacted]

10.5.6 Safety Analysis

All safety analyses will be performed on the safety population.

The safety of OC-01 (varenicline) will be assessed primarily by the incidence of AEs. An AE will be considered a treatment-emergent AE (TEAE) if it occurs or worsens on or after initiation of treatment. An overall summary of TEAEs will be presented including the number of events and the number of subjects with events (along with percentages) by treatment group for TEAEs in several categories base on seriousness, relationship to treatment, and severity.

Other safety endpoints including visual acuity, slit-lamp biomicroscopy and intranasal examination will be summarized by treatment group and visit using descriptive statistics. Changes or shifts from baseline will be summarized where appropriate. For assessments performed by eye, study eye and fellow eye will be summarized separately.

The SAP will present methods of analysis of these defined parameters in detail.

10.5.7 Interim Analysis

No interim analysis planned for this study.

11 COMPLIANCE WITH GOOD CLINICAL PRACTICES, ETHICAL CONSIDERATIONS, AND ADMINISTRATIVE ISSUES

This study will be conducted in compliance with the protocol, Good Clinical Practices, including the International Conference on Harmonization (ICH) Guidelines, and in general, consistent with the Declaration of Helsinki. In addition, all applicable local, state, and federal requirements relevant to the use of study drugs in the countries involved will be adhered to.

11.1 Protection of Human Subjects

11.1.1 Subject Informed Consent

Informed consent/assent must take place before any study specific procedures are initiated. Signed and dated written informed consent must be obtained from each subject and/or from the subject's parent or legal guardian prior to enrollment into the study. If the subject is under the legal age of consent, the consent form must be signed by a legal guardian or as required by state and/or local laws and regulations.

All informed consent/assent forms must be approved for use by the Sponsor and receive approval/favorable opinion from an IRB prior to their use. If the consent form requires revision (e.g., due to a protocol amendment or significant new safety information), it is the investigator's responsibility to ensure that the amended informed consent is reviewed and approved by [redacted] prior to submission to the governing IRB and that it is read, signed and dated by all subjects subsequently enrolled in the study as well as those currently enrolled in the study.

If informed consent is taken under special circumstances (oral informed consent), then the procedures to be followed must be determined by [redacted] and/or Sponsor and provided in writing by [redacted] and/or Sponsor prior to the consent process.

11.1.2 Institutional Review Board Approval

This study is to be conducted in accordance with IRB regulations [U.S. 21 Code of Federal regulations (CFR) Part 56.103]. The investigator must obtain appropriate IRB approval before initiating the study and re-approval at least annually.

Only an IRB-approved version of the informed consent form will be used.

11.2 Ethical Conduct of Study

This study will be conducted in accordance with the ethical principles that originated with the Declaration of Helsinki.

11.3 Subject Confidentiality

All personal study subject data collected and processed for the purposes of this study should be maintained by the investigator and his/her staff with adequate precautions so as to ensure the confidentiality of the data in accordance with local, state, and federal laws and regulations.

Monitors, auditors and other authorized representatives of [redacted] the Sponsor, the IRB approving this study, the Food and Drug Administration, the Department of Health and Human Services, other domestic government agencies, and other foreign regulatory agencies will be granted direct access to the study subject's original medical and study records for verification of the data and/or clinical trial procedures. Access to this information will be permitted to the aforementioned individuals to the extent permitted by law.

A report of the results of this study may be published or sent to the appropriate health authorities in any country in which the study drug may ultimately be marketed, but the subject's identity will not be disclosed in these documents.

11.4 Documentation

Source documents may include a subject's medical records, hospital charts, clinic charts, the investigator's study subject files, as well as the results of diagnostic tests such as X-rays, laboratory tests, and electrocardiograms. The investigator's copy of the CRFs serves as the investigator's record of a subject's study-related data.

11.4.1 Retention of Documentation

All study related correspondence, subject records, consent forms, record of the distribution and use of all study drug and copies of CRFs should be maintained on file for at least two years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region; or until at least two

years have elapsed since the formal discontinuation of clinical development of the study drug. These documents will be retained for a longer period if required by the applicable regulatory requirements or by an agreement with the Sponsor. It is the responsibility of the Sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

If the responsible investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping study records, custody must be transferred to a person who will accept the responsibility. The Sponsor must be notified in writing of the name and address of the new custodian.

11.5 Labeling, Packaging, Storage, Accountability, and Return or Disposal of Study Drug

11.5.1 Labeling/Packaging

Investigational drug will be provided in multi-use intranasal applicator that will be assigned at randomization for use during the first 28 days of study.

11.5.2 Storage of Investigational Drug / Placebo

The investigational drug / placebo must be stored in accordance with the pharmacy manual for this study, which contains detailed information regarding the storage and administration.

1.1.3 Accountability of Study Drug

The investigational drug / placebo is only prescribed by the principal investigator or his/her named sub investigator(s) and is to only be used in accordance with this protocol. The study drugs must only be distributed to subjects properly qualified under this protocol to receive study drug. The investigator must keep an accurate accounting of the study drugs by maintaining a detailed inventory. This includes the amount of study drugs received by the site, amount dispensed to subjects, amount returned to the site by the subjects, and the amount returned to the Sponsor upon the completion of the study.

11.5.2 Return or Disposal of Study Drug

You may be requested to destroy study drug or study drug kits on-site that are expired, not acceptable for use due to a temperature deviation, or at the end of the study. If site regulations do not permit destruction, study drugs will be returned to the Sponsor or their designee for destruction.

11.6 Recording of Data on Source Documents and Electronic Case Reports Forms

All subject data will be captured in the subject source documents which will be transcribed in the eCRFs. The investigator is responsible for ensuring that study data is completely and accurately recorded on each subject's eCRF, source documents, and all study-related materials. All study data should also be attributable, legible, contemporaneous, and original. A recorded datum should only be corrected in a manner that does not obliterate, destroy, or

render illegible the previous entry (e.g., by drawing a single line through the incorrect entry and writing the revision next to the corrected data). An individual who has corrected a data entry should make clear who made the correction and when, by adding to the correction his/her initials as well as the date of the correction.

Data entry of all enrolled and randomized subjects will use software that conforms to 21 CFR Part 11 requirements, and will be performed only by staff who have been trained on the system and have access to the system. Data will not be entered for screen failure subjects. An audit trail will be maintained within the electronic system to capture all changes made within the eCRF database. After the end of the study and database lock, electronic copies of all applicable subjects' eCRFs will be provided to each Investigator Site to be maintained on file by the Investigator.

11.7 Handling of Biological Specimens

Not applicable.

11.8 Publications

The study will be documented in a final report, which will contain appropriate statistical analysis and medical overview. No individual site or Investigator may publish or present any results from the study until the Sponsor completes a joint, multi-center publication of the trial results in conjunction with various participating Investigators and appropriate sites contributing data and comments. Subsequently, individual Investigators may request to publish or present results from the trial; however, approval will be at the sole discretion of the Sponsor. Should the foregoing language be in conflict with the language addressing publication in the clinical trial agreement, the language in the Clinical Trial Agreement will prevail.

12 REFERENCES

[redacted]

[redacted]

7-

[redacted]

[redacted]

13 APPENDICES

APPENDIX 1: SCHEDULE OF VISITS AND MEASUREMENTS

Procedure	Screen/ Visit 1 Day 1	Day 2-6	Visit 2 Day 7 ±2	Day 8-13	Visit 3 Week 2 Day 14 ±3	Day 15-27	Visit 4 Week 4 Day 28 ±4			Visit 5 Week 6 Day 42 ± 3	Visit 6 Week 24 Day 168 ±7	Visit 7 Week 48 Day 336 ±7	ET
							Visit 4a		Visit 4b (+3 days of 4a)				
							Pre-CAE®	Peri-CAE®	Schirmer's Test Evaluation				
Informed consent/HIPAA	X												
Demographics	X												
Medical history, prior medication(s), ocular history and updates	X												
Eligibility criteria	X												
Urine pregnancy test	X[1]						X[1]					X[1]	X[1]
OSDI© questionnaire	X												
Eye Dryness Score (EDS)	X		X		X		X	X[4]	X[6]				X
[redacted] Calibra® Ocular Discomfort Scale	X						X	X[4]					
BCVA	X[2]		X		X[2]		X		X[2]				X
Slit lamp biomicroscopy	X[2]		X		X[2]				X[2]	X	X	X	X
Corneal fluorescein staining	X								X[6]				X
Schirmer's test	X[2]				X				X[5]				
Schirmer's test with cotton swab stimulation	X												
Intranasal examination	X[2]		X						X[2]	X	X	X	X
Randomization	X												
Administer investigational drug / placebo	X[3]	X		X	X[3]	X		X	X[3]				
Diary Completion		X		X		X							
Dispense investigational drug / placebo	X				X		X						
Concomitant medications	X		X		X		X		X	X	X	X	X
AE Query	X		X		X		X		X	X	X	X	X

X[1] = For females of childbearing potential; X[2] = Pre- and Post-treatment procedures; X[3] = Concurrent with Schirmer's Test; X[4] = Procedure started at time 0 and then conducted every 5 minutes thereafter during the 120 minute CAE® exposure; X[5]= At Visit 4, Schirmer's Test Evaluation and CAE® procedures should be performed on different days within the visit window. The Schirmer's Test Evaluation and all assessments should be performed after the CAE® visit assessment. X[6]- Post Treatment Procedures. ET=Early Termination

APPENDIX 2: EXAMINATION PROCEDURES, TESTS, EQUIPMENT, AND TECHNIQUES

The following examination procedures, tests, equipment and techniques are listed in this Appendix:

Visual Acuity Procedures

LogMAR visual acuity must be assessed using an ETDRS chart. The procedure used will be consistent with the recommendations provided for using the ETDRS eye chart. Visual acuity should be evaluated at the beginning of each visit in the study (i.e., prior to slit lamp examination). Participants should use the most recent correction to attain their corrected distance visual acuity (CDVA); if they forget their spectacles, this prescription can be placed in a trial frame.

Equipment

The visual acuity chart to be used is the ETDRS chart. If smaller reproduction (18" by 18", e.g., from Prevent Blindness) wall charts are used, the participant viewing distance should be exactly 10 feet (or as specified by the manufacturer). In ALL cases, for purposes of standardizing the testing conditions during the study, all sites must use only ETDRS Series 2000 Chart 1 & 2, and the right eye should be tested first. For reflectance (wall) charts, the chart should be placed frontally and be well illuminated.

Measurement Technique

The chart should be at a comfortable viewing angle. The right eye should be tested first. The participant should attempt to read each letter, line-by-line, left to right, beginning with line 1 at the top of the chart. The participant should be told that the chart has letters only, no numbers. If the participant reads a number, s/he should be reminded that the chart contains no numbers, and the examiner should then request a letter in lieu of the number. The participant should be asked to read slowly, so as to achieve the best identification of each letter. S/he is not to proceed to the next letter until s/he has given a definite response.

If the participant changes a response (e.g., 'that was a "C" not an "O"') before s/he has read aloud the next letter, then the change must be accepted. If the participant changes a response having read the next letter, then the change is not accepted. The examiner should never point to the chart or to specific letters on the chart during the test.

A maximum effort should be made to identify each letter on the chart. When the participant says s/he cannot read a letter, s/he should be encouraged to guess. If the participant identifies a letter as one of two letters, s/he should be asked to choose one letter and, if necessary, to guess. When it becomes evident that no further meaningful readings can be made, despite encouragement to read or guess, the examiner should stop the test for that eye. However, all letters on the last line should be attempted as letter difficulties vary and the last may be the only one read correctly. The number of letters missed or read incorrectly should be noted.

LogMAR Visual Acuity Calculations

The last line in which a letter is read correctly will be taken as the base logMAR reading. To this value will be added the number "N x 0.02" where 'N' represents the total number of letters missed up to and including the last line read. This total sum represents the logMAR visual acuity for that eye.

Example: Participant correctly reads 4 of 5 letters on the 0.2 line, and 2 of 5 letters on the 0.1 line.

Base logMAR	= 0.1
N (total number of letters incorrect on line 0.2 as well as 0.1)	= 4
N x T (T=0.02)	= 0.08
Base logMAR + (N x T)	= 0.1 + 0.08
logMAR visual acuity	= 0.18

Repeat the procedure for the left eye.

In order to provide standardized and well-controlled assessments of visual acuity during the study, all visual acuity assessments at a single site must be consistently done using the same lighting conditions and same correction if possible during the entire study. If the same correction cannot be used (i.e., a participant broke his/her glasses), the reason for the change in correction should be documented.

Note: A clinically significant visual acuity decrease (defined as an increase of 0.32 or greater in logMAR score) from the Screening Visit (Visit 1) should be evaluated by the Investigator as a potential AE.

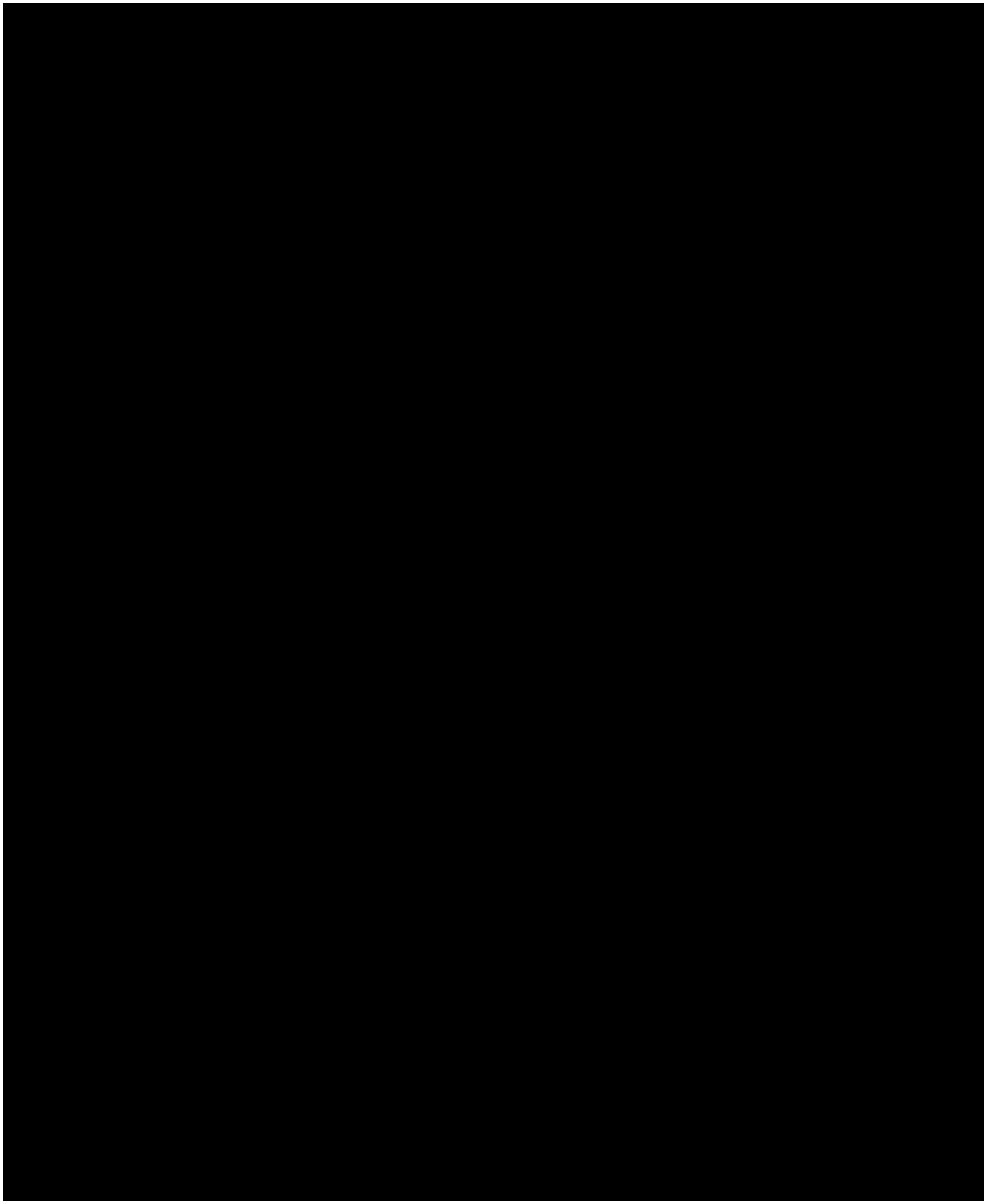
Slit Lamp Biomicroscopy

Slit lamp biomicroscopy will be performed during the study. Observations will be graded as *Normal* or *Abnormal*. Abnormal findings, which are clinically significant, will be described.

Corneal Fluorescein Staining

The examiner should instill 5 μL of 2% preservative-free sodium fluorescein solution into the inferior conjunctival cul-de-sac of each eye. Alternatively, corneal staining can be assessed using 1.0 mg sodium fluorescein strips. After moistening the tip of the strip with sterile buffered saline, the excess is shaken into a waste bin with a sharp flick. The lower lid is then pulled down and the flat end of the tip should be gently applied to the inferior tarsal conjunctiva with the intent of not inducing reflex tearing and instilling a very small volume of dye.

The participant will be instructed to blink naturally several times without forced closure of the eyelid to distribute the fluorescein. In order to achieve maximum fluorescence, the examiner should wait at least two minutes after instillation before evaluating corneal fluorescein staining. A Wratten #12 yellow filter will be used to enhance the ability to grade fluorescein staining. The staining will be graded with the NEI Scale. The upper eyelid is lifted slightly to grade the entire corneal surface.



Schirmer's Test with Topical Anesthesia

At the Screening Visit, one basal Schirmer's test will be performed followed by a Schirmer's test with cotton swab nasal stimulation. The Schirmer's test with topical anesthetic will be used to assess tear production using the following steps:

1. Topical anesthetic drops such as 0.5% proparacaine hydrochloride or equivalent should be instilled in both eyes of the participant.
2. The participant will be instructed to keep the eyes gently closed for one minute.
3. After opening the eyes and allowing the eyes to recover for approximately one additional minute, excess moisture in the inferior fornix is gently removed with a spear.
4. Schirmer's strips (35 mm x 5 mm size filter paper strip) will be placed in each eye at the junction of the middle and lateral thirds of the lower eye lid.
5. Under ambient light, the participant will be instructed to look forward and to blink normally during the course of the test. The test should be performed in a room with no direct air or sunlight on the participant's face.
6. The Schirmer's strips should remain in place until five minutes have elapsed or both strips have reached maximum score.
7. After five minutes, strips will be removed from both eyes and the amount of wetting will be recorded. The strips should be taped to the CRF.

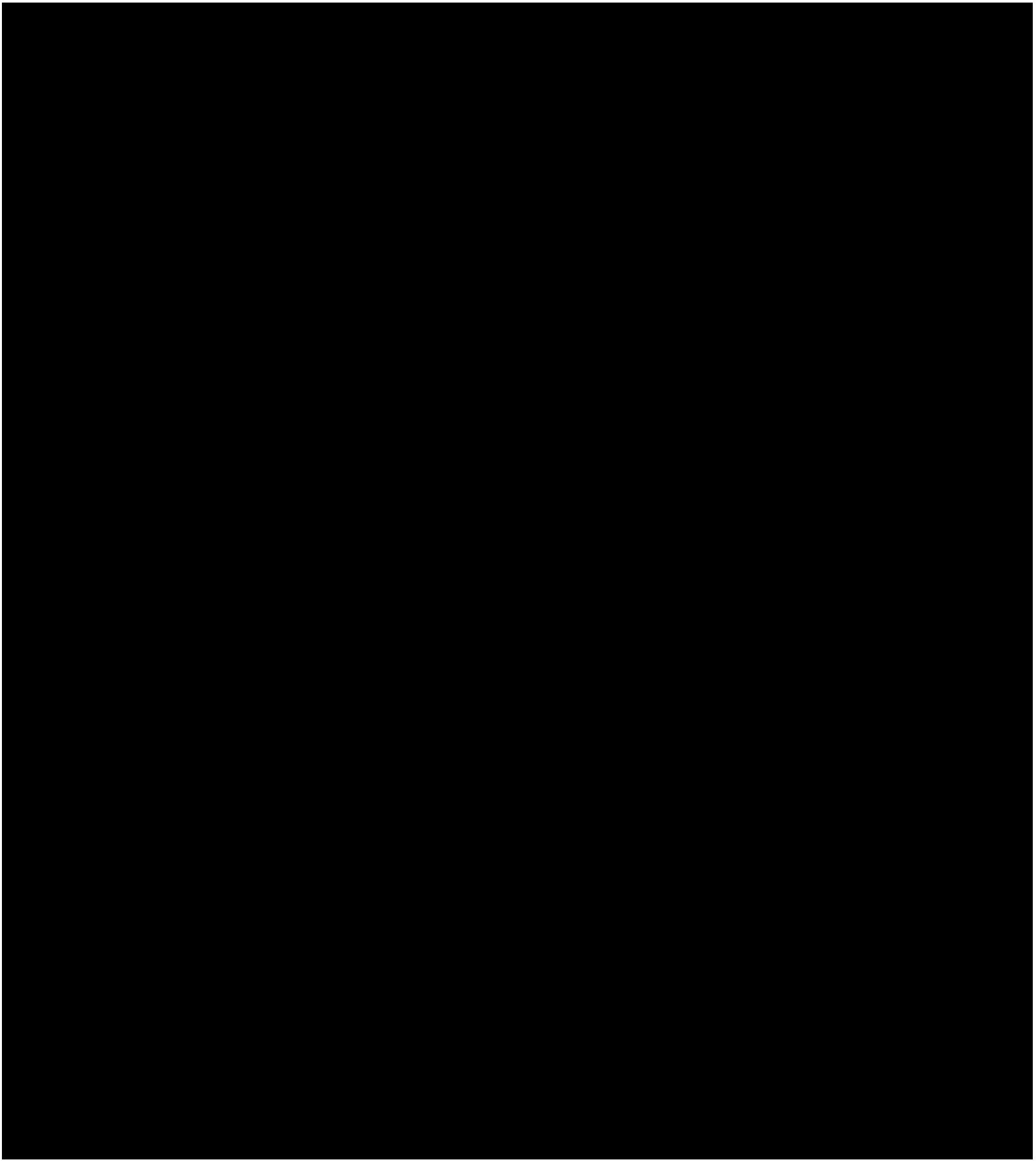
<u>Schirmer's test using cotton swab nasal stimulation</u>

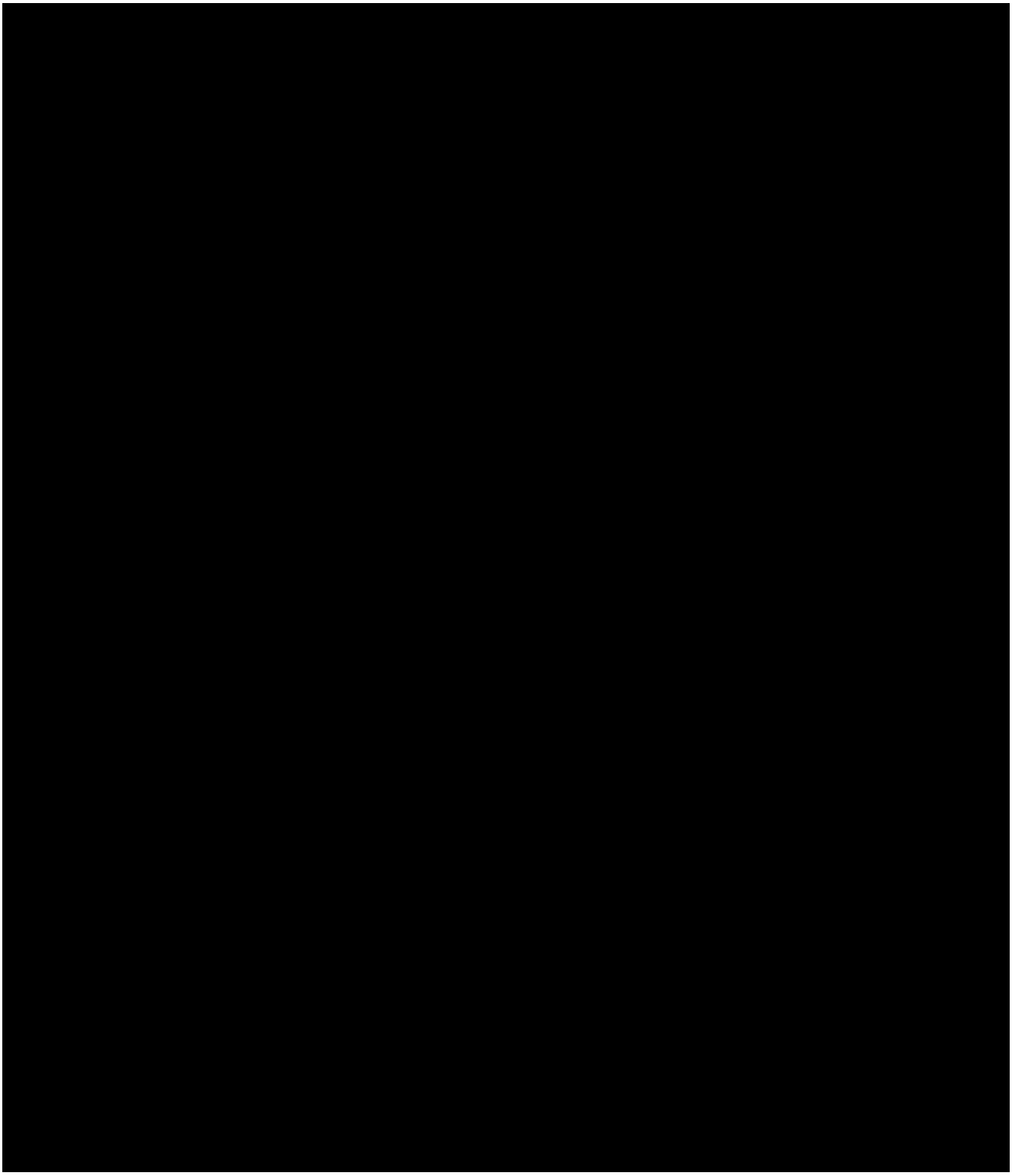
At the Screening Visit, the Schirmer's test should be performed using cotton swab nasal stimulation. New anesthetic drops should be instilled following the same procedure specified in steps #1 to 3 above.

1. With new strips in place, the examiner should insert cotton swabs in the participant's two nostrils simultaneously and gently probe both nasal middle turbinates for approximately 30 seconds. After this, the examiner can simply hold the swabs in place, applying gentle pressure, and repeat probing intermittently as necessary.
2. Alternatively, the participant can be instructed to hold the cotton swabs and gently probe both nasal turbinates simultaneously, resting intermittently before probing again. The examiner should continuously coach the participant on how to perform this test properly.
3. The Schirmer's strips should remain in place until five minutes have elapsed or both strips have reached maximum score.

Both Schirmer's scores will be recorded and verified that they meet the inclusion criteria.

[redacted]





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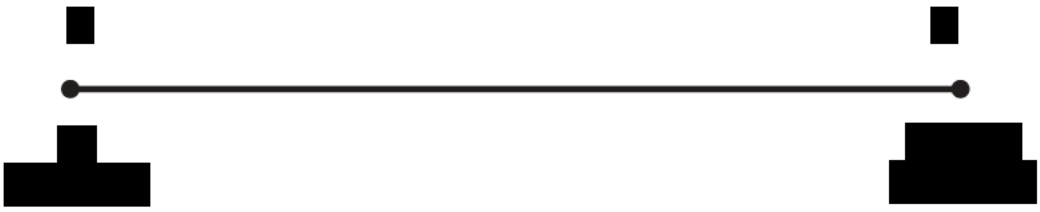

[redacted]

[redacted]

APPENDIX 3: SPONSOR AND [redacted] APPROVALS

Protocol Title: A Phase 3, Multicenter, Randomized, Controlled, Double-Masked, Clinical Trial to Evaluate the Efficacy and Safety of OC-01 (varenicline) Nasal Spray on Signs and Symptoms of Dry Eye Disease (The ONSET-2 Study)

Protocol Number: OPP-101

Signed: [redacted] Date: [redacted]

Oyster Point Pharma, Inc.

Signed: [redacted] Date: [redacted]

APPENDIX 4: INVESTIGATOR'S SIGNATURE

Protocol Title:	A Phase 3, Multicenter, Randomized, Controlled, Double-Masked, Clinical Trial to Evaluate the Efficacy and Safety of OC-01 (varenicline) Nasal Spray on Signs and Symptoms of Dry Eye Disease (The ONSET-2 Study)
Protocol Number:	OPP-101

I agree to implement and conduct the study diligently and in strict compliance with the protocol, good clinical practices and all applicable laws and regulations. I agree to maintain all information supplied by [redacted] and the Sponsor in confidence and, when this information is submitted to an Institutional Review Board (IRB) or another group, it will be submitted with a designation that the material is confidential.

I have read this protocol in its entirety, including the above statement, and I agree to all aspects.

Signed:_____ Date:_____

Name: _____

Title: _____

Site: _____

Address: _____

Phone Number: _____